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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/659,643	09/12/2000	James J. Gibbons Jr.	AM100081	6975

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/659,643	GIBBONS JR. ET AL.	
	Examiner	Art Unit	
	Dwayne C. Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28MAR2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 5-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1, 3, 5-7 are pending.

2. Claims 1, 3, 5-7 are rejected.

Response to Arguments

Applicants' arguments filed March 28, 2005 have been fully considered but they are not persuasive. Applicants argue the following points of issue. First, applicants argue that the Office Action of November 26, 2004 is defective in that the types of cases used for supporting the stance of unpredictability and undue breadth have a different fact pattern than the instant claims. Second, applicants submit that one skilled in the art would be enabled to practice the claimed subject matter with any and all cytokine inducers to treat every tumor and further along with any chemotherapeutic agent.

3. First, applicants argue that the Office Action of November 26, 2004 is defective in that the types of cases used for supporting the stance of unpredictability and undue breadth have a different fact pattern than the instant claims. However, the cases and rationale set forth in the previous Office Action clearly show that there is unpredictability in the art and that the instant specification does not enable one skilled in the art to predict the outcome of an unpredictable ailment such as cancer. In addition, the instant specification does not provide sufficient guidance, instruction, and even working examples to help enable the artisan with predicting the outcome of an ailment such as cancer, especially when the instant claims are written to treat any and all tumors with

any and all cytokine inducers of formula I and even further with any and all chemotherapeutic agents. Moreover, the single example in the entire specification does not provide enablement for all compounds of formula I nor does it provide guidance to treat any other cancer or tumor cell nor does the instant specification provide ample direction and teachings to utilize any other chemotherapeutic agent other than paclitaxel along with the sole exemplified cytokine inducer compound of formula I of [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-l-lysyl]-alanine or a pharmaceutically acceptable salt thereof.

4. Second, applicants submit that one skilled in the art would be enabled to practice the claimed subject matter with any and all cytokine inducers to treat every tumor and further along with any chemotherapeutic agent. The instant specification does not provide the skilled artisan with enablement to practice the full scope of the claims for every tumor and every cytokine inducer embraced by formula I and even with every possible combination with any chemotherapeutic agent. Accordingly, for these reasons and those of record one skilled in the art is not enable to practice the full scope of the instantly claimed subject matter.

Claim Rejections - 35 USC § 112

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The rejection of claims 1, 3, and 5-7 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the cytokine inducers compound of

formula I of [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof and only for the treatment of nonsmall cell type lung tumors and only with the coadministration with paclitaxel, does not reasonably provide enablement for using other cytokine inducers compounds and for the treatment of other types of tumors is maintained and repeated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to the cytokine inducers compound of formula I of [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof and only

for the treatment of nonsmall cell type lung tumors and only with the coadministration with paclitaxel.

(2) The state of the prior art

The compounds of the inventions are the cytokine inducers compound of formula I of [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof and only for the treatment of nonsmall cell type lung tumors and only with the coadministration with paclitaxel. However, the prior art does not teach that these tumors and cancer are highly unpredictable and consequently their treatment is also highly unpredictable to the artisan, see Stein, J. H.

(3) The relative skill of those in the art

The relative skill of those in the art of cancer pharmaceuticals is very high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements functioning the same in different circumstances, yielding predictable results, but chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24

(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of the cytokine inducers compound of formula I of [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof and only for the treatment of nonsmall cell type lung tumors and only with the coadministration with paclitaxel an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 1 is directed to the plethora of compounds of embraced by the formula I and the treatment of any solid tumor and that all compounds of formula I are effective with the coadministration of any chemotherapeutic agent. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991).

In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of all cytokine inducers of formula I and any chemotherapeutic agent to be effective in treating any and all tumors is insufficient for enablement. The specification provides no guidance, in the way of enablement for all

cytokine inducers compounds of formula I other than the compound of for the cytokine inducers compound of formula I of [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof, and only for the treatment of nonsmall cell type lung tumors and only with the coadministration with paclitaxel. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds that fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses the coadministration of a cytokine inducers of formula I along with any chemotherapeutic agent and for the treatment of any tumor. However, the instant specification only has enablement for only one cytokine inducers compound of formula I, namely [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof, and only for the treatment of nonsmall cell type lung tumors and only with the coadministration with paclitaxel, see page 6 of the instant specification.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine; or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the compounds that are embraced by the cytokines of formula I and additionally for the treatment of all tumors with the coadministration of any chemotherapeutic agent that would be enabled in this specification.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons support this rejection. First, Claim 1 recites the limitation "the -CH-X moiety" in the description of variables section for R_a and R_3. There is insufficient antecedent basis for this limitation in the claim. Second, it is unclear and confusing where the heteroatoms of oxygen and nitrogen are to be attached with "the -CH-X moiety". Third, "the -CH-X moiety" has an incomplete valency on the carbon atom of this moiety. For these reasons, one skilled in the art would consider these claims vague and indefinite.

Claim Rejections - 35 USC § 103

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Applicant has provided evidence in this file showing that the invention was owned by, or subject to an obligation of assignment to, the same entity as US Patent No. 5,545,662 at the time this invention was made, or was subject to a joint research agreement at the time this invention was made. However, reference US Patent No. 5,545,662 additionally qualifies as prior art under another subsection of 35 U.S.C. 102, and therefore, is not disqualified as prior art under 35 U.S.C. 103(c).

12. Applicant may overcome the applied art either by a showing under 37 CFR 1.132 that the invention disclosed therein was derived from the invention of this application, and is therefore, not the invention "by another," or by antedating the applied art under 37 CFR 1.131.

13. Accordingly, the rejection of claims 1, 3, and 5-7 under 35 U.S.C. 103(a) as being unpatentable over Ayral-Kaloustian et al. of U.S. Patent No. 5,545,662 in view of The Merck Index is maintained and repeated for both the above-stated and reasons of record. Ayral-Kaloustian et al. teach the urea and urethane compounds of Formula I, namely the compound No. 28, that is useful in the treatment of cancer. (see abstract). in addition, Ayral-Kaloustian et al. teach that these compounds are useful for their ability to induce cytokine formation and restore bone marrow after chemotherapy, (see column 17, lines 8-10). Ayral-Kaloustian et al. further teach the compound No. 28 is useful in

the treatment of cancer, (see column 19, lines 18-31). Moreover, the skilled artisan would have been motivated to especially use the cytokine inducers compound of formula I to treat cancer, (see abstract and column 19, lines 26-27 as well as the repeated example of the cytokine inducer of formula I, namely Compound No. 28) since this compound No. 28 appears repeatedly in many examples in Ayral-Kaloustian et al.

14. The Merck Index teaches of the following known anticancer agents: bleomycins, cisplatin, mitomycins, vinblastine, vincristine, (see pages 183, 329, 890-891, and 427-1428, respectively). The skilled artisan would have been motivated to select any known anticancer agent, such as paclitaxel, to treat cancer especially to obviate multi-drug resistance as well as decrease the toxicity level of a chemotherapeutic agent. Moreover, "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . .[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, the skilled artisan would have been motivated to combine two pharmaceuticals, which are known to treat the very same ailment, namely cancer, together. In addition, it is well known in the oncology art to use multiple agents having different modalities of action as part of a chemotherapy "cocktail" to offset drug resistance to the tumor(s) as well as increasing the therapeutic efficacy of the anti-cancer agents while minimizing the adverse and unwanted side effects.

15. The rejection of claims 1, 3, and 5-7 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,545,662 in view of The Merck Index is withdrawn in view of the remarks of March 28, 2005 presenting evidence of common ownership.

Obviousness-type Double Patenting

16. The rejection of claims 1, 3, and 5-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,545,662 in view of The Merck Index is removed in response to the remarks and Terminal Disclaimer of March 28, 2005.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, may be reached at (571) 272-0951. The official fax No. for correspondence is (703) 872-9306.

Also, please note that U.S. patents and U.S. patent application publications are no longer supplied with Office actions. Accordingly, the cited U.S. patents and patent application publications are available for download via the Office's PAIR, see http://pair-direct.uspto.gov. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

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DWAYNE JONES
PRIMARY EXAMINER

Tech. Ctr. 1614
June 23, 2005